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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/908,469	08/06/97	BACA M	P1093P1

HM12/1108

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EXAMINER	
HELMS, L	
ART UNIT	**PAPER NUMBER**
1642	31

DATE MAILED: 11/08/01

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/908,469	Applicant(s) BACA ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *1-33 and 39-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The request filed on 9/10/01 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 08/908,469 is acceptable and a RCE has been established. Claims 1-42 are pending and claims 34-38 are currently under prosecution. An action on the RCE follows.

2. Claim 34 has been amended.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be foound in a prior Office Action

4. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

5. The rejection of claims 34-38 under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al (WO 94/10202, published 5/11/94) is withdrawn in view of the new grounds of rejection.

Priority

6. The instant application claims priority to provisional application 60/126,446, filed 4/7/97. Newly amended claim 34 recites the limitation of "a Kd value of no more than about 1 X 10^{-8}M" and "has an ED50 value of no more than about 5 nM..." and "inhibits VEGF-induced angiogenesis in vivo, ... in an A673 in vivo tumor model". The limitations have support in the instant application, however, it appears that there is not support for

these limitations in the 60/126,446 application. As such the priority date granted to claims 34-38 is 8/6/97.

The following are some NEW GROUNDS of rejections.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 34-38 are rejected under 35 U.S.C. 102(a) as being anticipated by Baca et al (The Journal of Biological Chemistry 272:10678-10684, 4/18/97, IDS #14).

The claims recite an isolated nucleic acid encoding a humanized variant of a parent wherein said parent comprises a non-human variable domain and wherein the humanized variant binds human VEGF with a Kd of no more than about 1 X 10-8M said Kd value being no more than about 6 fold of the Kd of the parent, has an ED 50 of no more than about 5 nM for inhibiting VEGF-induced proliferation of endothelial cells in vitro, and inhibits VEGF-induced angiogenesis in vivo where 5mg/5kg inhibits at least 50% of tumor growth in an A673 in vivo tumor model, and vectors, host cells, a process of producing such antibody.

Baca et al teach a nucleic acid encoding a humanized anti-VEGF antibody which binds VEGF with a K_d value of no more than 1 X 10^{-8}M (see Table III, hu2.10V) and the

antibody binds about 6 fold the affinity of the parent antibody (see abstract). Baca et al's antibody appears to be the same as that claimed (hu 2.10V is the antibody discussed in the response filed 9/10/01, see pages 4-5 of response and disclosed in the specification (see page 67 in specification). The record does not contain any evidence that the referenced antibody does not differ in any significant manner to the claimed antibody. The record does not contain any evidence that the referenced antibody does not have the inherent properties of those claimed in claim 34, accordingly the nucleic acid of Baca et al encodes an antibody which is the same as that which is claimed.

Claim Rejections - 35 USC § 103

9. Claims 34-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al (WO 94/10202, published 5/11/94) and further in view of Adair et al (WO 91/09967, published 7/11/91, IDS#4) and Yelton et al (The Journal of Immunology 155:1994-2004, 1995).

The claims are summarized as a nucleic acid molecule that encodes a humanized anti-VEGF antibody which binds VEGF with a K_d value of no more than 1 X 10^{-8}M said Kd being no more that 6 fold of the Kd of the parent, wherein the antibody has an ED50 of no more than about 5nm for inhibiting VEGF-induced proliferation of endothelial cells in vitro, inhibits VEGF-induced angiogenesis, and inhibits at least 50% of tumor growth in a tumor model, and vectors, host cells, and methods of expressing the antibody.

Ferrara et al teach a nucleic acid molecule that encodes an anti-VEGF antibody (see abstract). Ferrara et al also teach a humanized antibody (see page 8, lines 13-31) and the effect of the antibodies in tumor cell growth and angiogenesis (see page 23-24 and page 4). Ferrara et al does not teach a specific method for humanization. This deficiency is made up for in the teachings of Adair et al.

Adair et al teach a method of antibody humainzation by CDR grafting and framework modifications (see abstract).

Yelton et al teach an affinity maturation method comprising alterations in the CDRs of the heavy chain (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a nucleic acid molecule that encodes a humanized the antibody of Ferrara et al by the methods of humanization of Adair et al and Yelton et al .

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a nucleic acid encoding a humanized anti-VEGF antibody because Adair et al teach a method for humanization of antibodies because "most Mabs are of rodent origin, they are naturally antigenic in humans and thus can give rise to an undesirable immune response termed the HAMA" (see page 2). In addition, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to produce a nucleic acid molecule that encodes a humanized anti-VEGF antibody because Ferrara et al teach the antibody can be humanized and the tumors from A4.6.1 treated animals were smaller than those tumors

in mice treated with a control antibody (see Figure 5). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a nucleic acid encoding a variant of a parent anti-VEGF antibody of Ferrara et al by the methods of Adair et al and Yelton et al because Yelton et al teach a method for affinity maturation of an antibody in order to "change the form, affinity, and potentially the specificity of Abs to optimize them for delivering a wide variety of therapeutic agents to tumor cells." (See page 2002 last paragraph) Moreover, it would have been obvious to humanize the A4.6.1 antibody of Ferrara et al by the methods of Adair et al and Yelton et al because Ferrara et al teach human VEGF and in view of Adair and Yelton et al it would be obvious to humanize the antibody for therapy.

It is the Examiner's position that the nucleic acid produced by humanizing Ferrara et al's antibody with Adair et al's and Yelton et al's method would produce a nucleic acid that would encode a humanized antibody that would have the binding and inhibition characteristics claimed. One of ordinary skill in the art would reasonably conclude that Ferrara et al's antibody humanized with Adair et al's and Yelton et al's method also possesses (1) the same binding affinity to the human VEGF, and (2) inhibits angiogenesis and tumor growth of at least about 50% in A673 in vivo tumor model, therefore, it appears that Ferrara et al's antibody humanized with Adair et al's and Yelton et al's method would produce a nucleic acid molecule that would encode a humanized antibody that is identical to the claimed nucleic acid. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed nucleic acid encoding a humanized antibody with the nucleic acid encoding the

humanized antibody of Ferrara et al's antibody humanized with Adair et al's and Yelton et al's method, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed nucleic acid and the nucleic acid of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 9/10/021 has been carefully considured but is deemed not to be persuasive. The response states that the unexpected nature of the present invention is illustrated by the inventors own initial work in that several attempts were made to produce the claimed nucleic acid encoding the antibody with the claimed properties. In response to this argument, the response is not commensurate in scope with claims. If applicants are claiming unexpected results then the claims should be directed to the hu2.01V species (F(ab)-12). Additionally, the response states that several affinity-improved variants also effectively blocked VEGF-induced endothelial cell proliferation in vitro (see page 5 of response). In view of this statement, it would seem that it was not unexpected to produce other high affinity antibodies. In fact, at the time the claimed invention was made improving antibody affinity was not unexpected as evidenced by Adair et al and Yelton et al cited above. It was known that CDR grafting alone often resulted in loss of affinity (which was done in the case of the hu2.0 antibody in the

instant application) and that methods of Adair et al and Yelton et al were used to improve affinity for antibodies to 1 X 10^{-8}M or better.

Conclusions

10. No Claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela J. Huff

SHEELA HUFF
PRIMARY EXAMINER